DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

James L. Gaskill, PharmD
Director, Promotional Regulatory Affairs
AstraZeneca LP
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

RE: NDA 022047
SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets
MACMIS #18866

Dear Dr. Gaskill:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed AstraZeneca LP's (AZ) MDD (major depressive disorder) leave behind sheet 1 2010 (281061) (leave behind sheet) for its drug product, SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets (Seroquel XR). The leave behind sheet is misleading because it overstates the efficacy of Seroquel XR and omits material facts and risks associated with the drug. Thus, the leave behind sheet misbrands Seroquel XR in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(6)(i) & (e)(7)(i).

Background

The Indications and Usage section of the FDA-approved product labeling (PI) for Seroquel XR states the following (in pertinent part; emphasis in original):

> **Adjunctive Treatment of Major Depressive Disorder (MDD)**
> SEROQUEL XR is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD. The efficacy of SEROQUEL XR as adjunctive therapy to antidepressants in MDD was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant treatment. . . .

Additionally, the PI for Seroquel XR includes multiple risks. The PI contains Boxed Warnings regarding increased mortality in elderly patients with dementia-related psychosis and the risk of suicidality and antidepressant drugs. Seroquel XR also has numerous Warnings and Precautions including: neuroleptic malignant syndrome, hyperglycemia and diabetes mellitus, hyperlipidemia, weight gain, tardive dyskinesia, orthostatic hypotension, increases in blood pressure in children and adolescents, leuokopenia, neutropenia and agranulocytosis, cataracts, seizures, hypothyroidism, hyperprolactinemia, transaminase elevations, potential for cognitive and motor impairment, priapism, disruption of body temperature regulation, dysphagia, limited clinical experience in patients with certain concomitant illness, and withdrawal symptoms. According to the Adverse Reactions section of the PI, in the 6-week, placebo-controlled, fixed-dose adjunctive therapy clinical trials for MDD, the most commonly

observed adverse reactions associated with the use of Seroquel XR (incidence of ≥5% and observed at a rate at least twice that of placebo) were somnolence (150 mg: 37%; 300 mg: 43%), dry mouth (150 mg: 27%; 300 mg: 40%), fatigue (150 mg: 14%; 300 mg: 11%), and constipation (150 mg only: 11%).

The Clinical Studies section of the PI states that the efficacy of Seroquel XR as adjunctive therapy in the treatment of MDD was demonstrated in two 6-week, placebo-controlled, fixed-dose trials. The primary endpoint in these trials was change from baseline to week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score). Seroquel XR 300 mg/day as adjunctive treatment to other antidepressant therapy was superior to antidepressant alone in reduction of MADRS total score in both trials; Seroquel XR 150 mg/day as adjunctive treatment was superior to antidepressant therapy alone in reduction of MADRS total score in one trial.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Page 2 of the leave behind sheet includes the following claims (underlined emphasis added):

- "*Achieving remission is difficult. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, nearly 63% of patients did not achieve remission with initial antidepressant treatment*."[1]

Page 3 of the leave behind sheet also presents the headline claim, "**APPROXIMATELY 50% GREATER REMISSION RATES (MADRS Total Score ≤8) SEROQUEL XR PLUS AN ANTIDEPRESSANT VS AN ANTIDEPRESSANT* ALONE AT WEEK 6**"[2] (underlined emphasis added) in conjunction with a graph titled, "**REMISSION RATES: MDD**"[2,a] (underlined emphasis added) which presents the percentage of patients with MADRS Total Score ≤8 at week 6 for patients treated with Seroquel XR 150 mg/day + AD (antidepressant) (n=309, 35.6%), Seroquel XR 300 mg/day + AD (n=307, 36.5%), and placebo + AD (n=303, 24.1%). Accompanying the graph are the following claims (underlined emphasis added):

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[1] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.

[*] In studies of SEROQUEL XR as adjunctive therapy in the treatment of MDD, patients were treated with one of the following antidepressants prior to study entry: the SSRIs Paxil® (paroxetine), Prozac® (fluoxetine), Zoloft® (sertraline), Lexapro® (escitalopram), or Celexa® (citalopram); the SNRIs Cymbalta® (duloxetine) and Effexor® (venlafaxine); the TCA amitriptyline; and Wellbutrin® (bupropion) (footnote omitted).

[2] Data on file, 265018, AstraZeneca Pharmaceuticals LP.

[a] Data combined from two 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled adjunctive therapy trials in the treatment of patients with MDD who had an inadequate response to at least one AD.

- "**~50%** → greater remission rates at Week 6 with SEROQUEL XR + AD vs an AD used alone"[2]

- "**For these studies, remission was defined conservatively as Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score ≤8 at Week 6**"[2]

- "In Study 6, SEROQUEL XR 300 mg/day + AD demonstrated significantly greater remission rates vs placebo + AD at Week 6 (42.5% vs 24.5%, respectively; *P*<0.01)"[2]
  - "SEROQUEL XR 150 mg/day + AD did not achieve statistical significance vs placebo + AD at Week 6 in this study (35.0% vs 24.5%, respectively)"[2]

- "In Study 7, SEROQUEL XR 150 mg/day + AD demonstrated significantly greater remission rates vs placebo + AD at Week 6 (36.1% vs 23.8%, respectively; *P*<0.05)"[3]
  - "SEROQUEL XR 300 mg/day + AD did not achieve statistical significance vs placebo + AD at Week 6 in this study (31.1% vs 23.8%, respectively)"[3]

These claims misleadingly suggest that patients will achieve "remission" with Seroquel XR plus antidepressant versus antidepressant alone, when this has not been demonstrated by substantial evidence or substantial clinical experience. The referenced studies are not considered substantial evidence to support claims of "remission." "Remission" was not specified as a primary or key secondary measure in these study protocols. Furthermore, six weeks is not a long enough time period to adequately assess "remission." Moreover, there is no regulatory definition or criteria on how to define "remission" in MDD.

Page 2 of the leave behind sheet presents the case study of "***Catherine F.***," a patient who is "**still experiencing unresolved symptoms of MDD including sadness and loss of Interest***" (emphasis in original). This presentation misleadingly suggests that Seroquel XR alleviates the specific MDD symptoms of sadness and loss of interest, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the Clinical Studies – Major Depressive Disorder, Adjunctive Therapy to Antidepressants section of the PI, the efficacy of Seroquel XR was measured using a total score (i.e., "The primary endpoint in these trials was change from baseline to week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item clinician rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) with total scores ranging from 0 (no depressive features) to 60 (maximum score)."). Thus, while Seroquel XR has been shown to improve the total MADRS score, the clinical trials were not designed to assess the impact of Seroquel XR on each individual domain of the MADRS instrument. The inclusion of the accompanying footnote, "*Sadness and loss of interest are select symptoms of MDD based on *DSM-IV-TR* criteria" does not mitigate the misleading nature of this presentation.

[3] Bauer M, Pretorious HW, Constant EL, et al. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *J Clin Psychiatry*. 2009;70(4):540-549.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

Page 3 of the leave behind sheet includes the following claims (emphasis added):

- "Proven effective in MDD as add-on therapy compared to an AD alone"[4]
  - "Primary end point measured at Week 6 with significant improvement in MADRS Total Score as early as Week 1."[5]

This presentation is misleading because it omits material facts about Seroquel XR. Specifically, it fails to disclose that only the 300 mg dosage strength provided a significant improvement in MADRS Total Score at week 1, thus misleadingly implying that the 150 mg dosage strength also achieved this effect.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The leave behind sheet omits material information from a number of risks associated with Seroquel XR, including neuroleptic malignant syndrome, hyperglycemia and diabetes mellitus, and potential for cognitive and motor impairment. For example, while the leave behind sheet includes a discussion of the risk of tardive dyskinesia, it fails to state that the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Also, while the leave behind sheet states that the Warning and Precautions section of the Seroquel XR PI includes the risk of seizures, it fails to state that Seroquel XR should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Please note that this is not an exhaustive list.

Conclusion and Requested Action

For the reasons discusses above, the leave behind sheet misbrands Seroquel XR in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(6)(i) & (e)(7)(i).

DDMAC requests that AZ immediately cease the dissemination of violative promotional materials for Seroquel XR, such as those described above. Please submit a written response to this letter on or before August 13, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Seroquel XR that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug

[4] SEROQUEL XR Prescribing Information.
[5] Data on file, 265023, AstraZeneca Pharmaceuticals LP.

Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18866 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Seroquel XR comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22047	ORIG-1	ASTRAZENECA PHARMACEUTICALS LP	SEROQUEL XR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHELLE L SAFARIK
07/29/2010